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GENERAL QUESTIONS

What is CTCAE (Common Terminology Criteria for Adverse Events)?

CTCAE is a list of adverse event (AE) terms commonly encountered in oncology. Each AE term is defined and accompanied by a grading scale that indicates the severity of the AE. In the new CTCAE v4.0, the AE terms are organized by the System Organ Classes (SOCs) defined by the Medical Dictionary for Regulatory Activities (MedDRA). CTCAE has been developed from the earlier vocabulary known as CTC (Common Toxicity Criteria).

What is CTC (Common Toxicity Criteria)?

CTC is the precursor of what is today named the Common Terminology Criteria for Adverse Events (CTCAE). The original CTC was developed by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) in 1983 to aid in the documentation and analysis of adverse effects of chemotherapy. CTC, like CTCAE, included terms and a severity grading scale with descriptions of the allowed grades of each term.

What is the rationale and purpose of CTCAE?

Adverse events are common phenomena affecting patients being treated for cancer. With the availability of new agents and the multimodality interventions, it is critical to monitor systematically the AEs that are linked to oncology research. CTCAE is fundamentally intended to be an agreed upon terminology for the designation, reporting and grading of AEs that occur in oncology research.

CTCAE serves several purposes:

- To standardize AE reporting within the NCI oncology research community, across groups and modalities
- To facilitate the evaluation of new cancer therapies, treatment modalities, and supportive measures
- To aid in AE recognition and severity grading
- To monitor safety data and for regulatory reporting
- To define oncology research protocol parameters (e.g., eligibility criteria; dose limiting toxicity; maximum tolerated dose; dose modification)

Why was a new version (4.0) of CTCAE released in May 2009?

Since the publication of CTCAE v3.0 in 2003, much new information has become available in the prevention, diagnosis, and treatment of cancer. Simultaneously, rapidly evolving information technology systems for biotech research and the caBIG® initiative have elucidated the necessity for data standardization. The new CTCAE v4.0 not only includes the appropriate new information, but also its terminology and organization are harmonized with MedDRA (Medical Dictionary for Regulatory Activities) in compliance with the data standardization objective.

What is MedDRA (Medical Dictionary for Regulatory Activities)?

MedDRA is the clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry throughout the entire regulatory process.

MedDRA is the adverse event classification dictionary endorsed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

How do the CTCAE and the MedDRA terminologies differ?

MedDRA is a hierarchical list of over 66,000 LLTs (Lowest Level Terms), is multi-disciplinary, and is clinically validated.
MedDRA terms are not associated with definitions or rating scales. MedDRA is available in nine languages (including English) and has a well established system of governance, the MedDRA MSSO (Maintenance Service and Support Organization). See MeDRA.

CTCAE is a list of terms commonly encountered in oncology interventions. Each AE term is defined and associated with a rating scale of severity. The rating scale is used in the definition of protocols parameters (Eligibility; Maximum Tolerated Dose; Dose modification; etc) and indicates what is reasonable to document, report, and analyze for patient safety oversight based on current oncology research interventions. CTCAE is available only in English.

What are the major differences between v3.0 and v4.0 of CTCAE?

The most obvious difference is the label/name of the highest level of CTCAE organization:

- CTCAE v3.0 was organized by CATEGORIES based on pathophysiology (e.g., ALLERGY/IMMUNOLOGY) or anatomy (e.g., DERMATOLOGY/SKIN).
- CTCAE v4.0 AE terms are MedDRA LLTs (Lowest Level Terms) which are listed based on their MedDRA primary SOC (System Organ Class); (e.g., Immune system disorders; Skin and subcutaneous tissue disorders).

The count of AE terms is less in CTCAE v4.0 than it was in CTCAE v3.0:

- CTCAE v3.0 listed 1,059 AE terms (28 of which were 'Other, specify')
- CTCAE v4.0 lists 790 AE terms (26 of which are 'Other, specify')

The most important difference is CTCAE v4.0 harmonization with MedDRA LLTs:

- CTCAE v3.0 listed many multi-concept terms (e.g., Fatigue (asthenia, lethargy, malaise)).
- CTCAE v4.0 lists only single-concept, valid MedDRA LLTs (e.g., Fatigue; Malaise; Lethargy)
- See the FAQ section "Adverse Event Terms" for more details.

What was the major issue related to AE terms when revising CTCAE v3.0 for the v4.0 release?

Mapping terms to MedDRA was the major issue. Although CTCAE v3.0 terms were mapped where possible to MedDRA LLTs, the mapping was imprecise, either because the CTCAE v3.0 term is a combination term (multiple concepts) or the term does not fulfill the standard conventions of MedDRA.

With which version of MedDRA was CTCAE v4.0 harmonized?

CTCAE v4.0 (release date May 2009) was harmonized with MedDRA Version 12.0.

What impact will MedDRA semi-annual releases have on CTCAE in the future?

CTCAE will be harmonized with MedDRA annually to coincide with the MedDRA complex release in March. With each MedDRA complex release, although unlikely, there may be very limited modifications to a CTCAE (MedDRA LLT) term or code which will not impact the medical/clinical content or interpretation of CTCAE.

How often is CTCAE updated?

Major CTCAE version updates are anticipated to occur no more often than every two years. Each time a major version of CTCAE is released it will be harmonized with the latest version of MedDRA.

Licensing and using CTCAE

What is the official reference citation for CTCAE v4.0?

National Cancer Institute
Common Terminology Criteria for Adverse Events v4.0
NCI, NIH, DHHS. May 29, 2009
NIH publication # 09-7473

Are there any CTCAE redistribution restrictions related to copyright?

CTCAE is not subject to copyright restrictions. It is developed and written by government employees at the National Cancer Institute (NCI), and therefore is in the public domain. One does not need special permission to reproduce or translate written text created by NCI staff.

Does NCI allow pharmaceutical companies, Clinical Research Organization, or others to reprint CTCAE v4.0 booklets?

Yes. NCI requests simply that notification of reprinting be sent to NCICTCAEHelp@mail.nih.gov. CTCAE is not subject to copyright restrictions, as explained above.

CTCAE current files are available at http://evs.nci.nih.gov/ftp1/CTCAE

CTCAE FAQ and other resources are available at
http://biomedgt.nci.nih.gov/wiki/index.php/CTCAE4

Because CTCAE is harmonized with MedDRA and MedDRA is a licensed product, is a site or investigator required to purchase a MedDRA license?

NCI has an extended license with MedDRA MSSO; under this license, the use of MedDRA is restricted to NCI studies. When CTCAE is used for NCI purposes only, there is no cost or requirement to purchase a MedDRA license.

Does the NCI MedDRA license extend to NCI partners (e.g., PhRMA companies)?

The NCI MedDRA license covers external research partners only when they are doing work directly for NCI. Hence if the work under that NCI contract required use of MedDRA, the user is covered, but only for the work under the NCI contract or agreement. The NCI license provides no coverage for any work done under contract outside the NCI.

While NCI has access to the MedDRA browser, the license agreement does not provide MedDRA browser access or MedDRA services (e.g., SMQs) to NCI contract holders, groups, sites, etc. Under the NCI MedDRA license, the MSSO has allowed:

- NCI to publish Excel documents of the mapping
- NCI to allow its contractors, groups and collaborators to utilize the MedDRA mappings in local databases
- NCI sites to analyze data using the MedDRA subset of mappings for CTEP List of Values (LOVs)

Who determines if a protocol is to be updated to the most recent version of CTCAE?

As of May 29, 2009, CTCAE v4.0 is available for use. Sponsors, sites, and/or investigators determine whether to use CTCAE for Adverse Event (AE) reporting within protocols, which CTCAE version to use, and when a protocol changes from one CTCAE version to another.

CTEP is in the process of mapping CTCAE v3.0 terms and grades, to CTCAE v4.0. Recommendations to consider regarding implementation of CTCAE v4.0:

- If the protocol is a CTEP study, continue as is until CTEP announces a timeline and process for updating to CTCAE v4.0.
- If the protocol is a non-CTEP study, check with the sponsor and/or investigator.

Is CTCAE used outside cancer trials?

CTCAE is designed to be used a tool to assess toxicity in oncology therapeutic trials. The NCI does, however, have anecdotal information that CTCAE is used in other medical disciplines. In April 2006 during a MedDRA MSSO (Maintenance Services and Support Organization) BRP (Blue Ribbon Panel) Meeting to discuss CTCAE and MedDRA issues, industry participants shared that CTCAE was

being used for AIDS/HIV trials, hypertension trials, and others. During the CTCAE Revision Project, some industry participants shared that CTCAE was going to be used for trials outside cancer. CTCAE is in the Public Domain and because NCI does not require registration for CTCAE use, specific information about the use of CTCAE outside of cancer is not available.

Organization of the terminology

How are CATEGORIES, which were used to organize AEs in CTCAE v3.0, different from MedDRA SOCs, which are used to organize AEs in CTCAE v4.0?

CATEGORIES are based on pathophysiology (e.g., ALLERGY/IMMUNOLOGY) or anatomy (e.g., DERMATOLOGY/SKIN). CTCAE v3.0 included 28 CATEGORIES. The MedDRA SOC organization aggregates related terms in medically meaningful groupings. MedDRA includes 26 SOCs. Most of the CTCAE v3.0 CATEGORIES were a one-to-one match with MedDRA SOCs: For example:

CTCAE v3.0 CATEGORY	MedDRA SOC
GASTROINTESTINAL	Gastrointestinal disorders
INFECTION	Infections and infestations
DERMATOLOGY/SKIN	Skin and subcutaneous tissue disorders
OCULAR/VISUAL	Eye disorders

Which CTCAE v3.0 CATEGORIES are deleted from (do not appear in) CTCAE v4.0?

Five CTCAE v3.0 CATEGORIES do not appear in CTCAE v4.0. These CATEGORY names are broad and non-specific and include AE terms associated with multiple SOCs.

1. DEATH
2. GROWTH AND DEVELOPMENT
3. HEMORRHAGE/BLEEDING
4. PAIN
5. SYNDROMES

For example, the CTCAE v3.0 HEMORRHAGE/BLEEDING CATEGORY, rather than listing AE terms according to body system or organ, includes AE terms for CNS, gastrointestinal, genitourinary, pulmonary, skin hemorrhages. By contrast, CTCAE v4.0 includes 42 hemorrhage terms listed in the following nine primary SOCs:

1. Eye disorders

2. Gastrointestinal disorders
3. Hepatobiliary disorders
4. Injury, poisoning and procedural complications
5. Nervous system disorders
6. Renal and urinary disorders
7. Respiratory, thoracic and mediastinal disorders
8. Reproductive system and breast disorders
9. Vascular disorders

Will a provision for ?Other, specify? remain in CTCAE?

Yes. CTCAE v4.0 is organized by MedDRA SOC (System Organ Class), and in each of the 26 SOCs, ?Other, specify? is a placeholder, an option for reporting a text/verbatim term.

Adverse Event Terms

Why are fewer AE terms in CTCAE v4.0 than in CTCAE v3.0?

CTCAE v4.0 lists 790 AE terms (26 of which are ?Other, specify?), compared to the 1,059 AE terms (28 of which were ?Other, specify?) in CTCAE v3.0. Terms were deleted for any of these reasons:

- They were rarely or never reported.
- They were duplicates (e.g., Pharyngeal ---listed in the GASTROINTESTINAL and in the PULMONARY CATGORIES).
- Medical concepts were identified that better represent the AE in current oncology research or practice.
- About 28% of the terms were multiple concepts only one of which, where possible, was mapped to a MedDRA term. Examples:

    - v3.0 Fatigue (malaise, lethargy, asthenia) mapped to MedDRA Fatigue. By contrast, in v4.0, three separate AE terms (MedDRA LLTs) are listed and graded: Fatigue; Malaise; Lethargy.
    - v3.0 Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) ? Select was accompanied by a list of 77 sites of infection (Abdomen; Bile duct; Bone; etc.). Each v3.0 infection term combined neutrophil count with the site of infection. None of the 77 combined terms harmonized with MedDRA. By contrast, the v4.0 Infection terms are single-concept MedDRA infection terms. Neutrophil count is listed and graded separately.

What are the sources of new AE terms in CTCAE v4.0?

CTCAE v4.0 AE includes new terms resulting from splitting multi-concept terms, supplying concepts that were missing from v3.0, and identifying new concepts occurring in current oncology interventions. Some examples:

- v3.0 multi-concept terms were split in v4.0:
    - ♦ Fatigue (malaise, lethargy, asthenia) was split into three v4.0 AE terms: Fatigue; Malaise; Lethargy
    - ♦ Abdominal distention/bloating was split into two v4.0 AE terms: Abdominal distention; Bloating
- v3.0 missing concepts were added in v4.0:
    - ♦ Unintended pregnancy
    - ♦ Sleep apnea
- New concepts were added in v4.0:
    - ♦ Papulopustular rash
    - ♦ Reversible posterior leukoencephalopathy syndrome

Why is each v4.0 AE term defined and what is the source of the definitions?

The same medical term is often understood differently by different people, and some terms may be misunderstood. To promote consistent description and understanding of adverse events, CTCAE v4.0 has adopted the policy of including text definitions for each AE term. This policy is a caBIG® standard supported by NCI for all biomedical terminology.

Definitions were initially drawn from NCI Thesaurus, which has matching concepts for all CTCAE AE terms. These definitions were thoroughly reviewed and modified to meet the needs of CTCAE users, focusing on those features most important in correctly describing adverse events. Experience and user feedback will help guide future development of AE text definitions.

Where are CTCAE v4.0 AE term synonyms? How are the ?Related terms? in CTCAE to be used?

CTCAE v4.0 terms are MedDRA Lowest Level Terms (LLTs). While some MedDRA LLTs might be considered synonyms, and other terms exist that might also be added as synonyms, criteria for such assertions have not yet been developed. The rules for adverse event reporting require extra caution, so such assertions should be avoided. Decisions about identifying synonyms are expected before the next major CTCAE release.

Rather than indicating synonyms, CTCAE v4.0 identifies ?Related terms.? The vast majority of CTCAE terms, which are MedDRA LLTs, are also MedDRA Preferred Terms (PTs). MedDRA PTs

include a group of LLTs with closely related meaning for describing adverse events. For the initial 4.0 release, CTCAE terms that match MedDRA PTs include a listing of the LLTs that are grouped with it in MedDRA. These groupings are intended to help CTCAE users find appropriate CTCAE AE terms. In a few cases a CTCAE v4.0 LLT is not a MedDRA PT, and in other cases CTCAE lists more than one LLT associated with a single PT. Designation of related terms for these cases will be evaluated on a case-by-case basis.

Why does the Short Name in CTCAE v3.0 no longer exist in CTCAE v4.0?

The Short Name facilitated hand entry of AE terms on paper Case Report Forms. It was useful in CTCAE v3.0 because some terms were multiple concepts and/or phrases. The Short Name is no longer needed because CTCAE v4.0 is harmonized with MedDRA LLTs, single-concept terms which are easier to record on paper.

Why do the Supra-ordinate terms in CTCAE v3.0 no longer exist in CTCAE v4.0?

A Supra-ordinate term in CTCAE v3.0 serves as a grouping term based on disease process, signs, symptoms, or diagnosis. A Supra-ordinate term is followed by the word ?Select? and is accompanied by specific AEs that are all related to the Supra-ordinate term. By contrast, CTCAE v4.0 does not group the AEs this way, but rather places each AE, as a MedDRA LLT, in its appropriate System Organ Class (SOC). The CTCAE v3.0 Supra-ordinate terms are not MedDRA LLTs and therefore are not used in CTCAE v4.0.
For example, CTCAE v3.0 PAIN CATEGORY includes one Supra-ordinate term followed by a list of many specific sites of pain. All sites use the same grading scale. CTCAE v4.0, however, includes 52 pain AE terms located across 14 MedDRA SOCs.

Grading Scale (Severity)

What are the general guidelines that define the grading scale (indicators of severity)?

To achieve internal consistency of grading scales across SOCs (System Organ Class), general guidelines for grade descriptions apply:
Grade 0 No Adverse Event

- Sign/symptom within normal limits

Grade 1 Mild Adverse Event (any of the following)

- Minor
- Mild symptoms and intervention not indicated
- Non-prescription intervention indicated
- No specific medical intervention
- Asymptomatic laboratory finding only
- Radiographic finding only
- Marginal clinical relevance

Grade 2 Moderate Adverse Event (any of the following)

- Intervention indicated
- Minimal, local, noninvasive intervention (e.g. packing, cautery)
- Limiting instrumental ADL (e.g., shopping; laundry; transportation; ability to conduct finances)

Grade 3 Severe Adverse Event (any of the following)

- Medically significant but not life-threatening
- Inpatient or prolongation of hospitalization indicated
- Important medical event that does not result in hospitalization but may jeopardize the patient or may require intervention either
    - ♦ to prevent hospitalization or
    - ♦ to prevent the AE from becoming life-threatening or potentially resulting in death
- Disabling - results in persistent or significant disability or incapacity
- Limiting self care ADL (e.g., getting in and out of bed; dressing; eating; getting around inside; bathing; using the toilet)

Grade 4 Life-threatening Adverse Event (any of the following)

- Life-threatening consequences
- Urgent intervention indicated
- Urgent operative intervention indicated
- Patient is at risk of death at the time of the event if immediate intervention is not undertaken

Grade 5 Fatal Adverse Event

- Death

What is the difference between ?serious? in the FDA?s definition and the severity grading scale in CTCAE?

?Serious? and ?severe? are not the same. ?Serious? is based on patient outcome, or action criteria associated with AEs that pose a threat to a patient?s life or functioning. On the other hand, ?severe? describes the intensity (severity) of a specific AE(as in mild, moderate, severe myocardial infarction); the AE itself, however, may be of relatively minor medical significance, such as severe headache, and therefore is not serious.

The CTCAE grading scale describes severity, not seriousness. Most AEs in CTCAE include clinical criteria that describe patient/event outcomes or indicated interventions to more clearly substantiate severity.

Seriousness, not severity, serves as a guide for defining FDA regulatory reporting obligations.

Note this definition in Code of Federal Regulations; Title 21, Volume 5; Revised as of April 1, 2008; CITE:
21CFR310.305:?Serious adverse drug experience - Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.?

What does a semicolon mean within the description of grades?

A semicolon is read as ?or? within the description of a grade. The highest grade is to be assigned when a clinical finding/situation fulfills any of the conditions separated by a semicolon in the grade descriptions. Example AE term Body odor, Grade 2: Pronounced odor; psychosocial impact; patient seeks medical intervention; Is read as ?Pronounced odor or psychosocial impact or patient seeks medical intervention?

Why does a dash (?) appear for some grades for some AE terms?

All grades are not appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection. An em dash (?) indicates a grade is not available or appropriate for a given AE term. Example: Palpitation is associated with Grades 1 and 2 only.

How is ?hospitalization? in the CTCAE grading scales different from ?hospitalization? in the ICH and regulatory sense?

CTCAE v4.0 uses ?hospitalization? as one indicator for severity. The general description for Grade 3 Severe Adverse Event includes ?inpatient or prolongation of hospitalization indicated.? Inpatient hospitalization includes any overnight stay in a health care facility, including the so-called ?23-hour observation? status often used because of insurance reimbursement issues. It does not include extended infusions or treatments in an outpatient facility. Evaluation and treatment in an emergency medical department is not per se a hospitalization, but investigators must use good judgment when considering reporting guidelines and definitions for a patient treated for extended periods of time in emergency departments. Prolongation of hospitalization (longer than expected) leading to a Grade 3 is appropriate when the hospitalization is the result of either the AE itself, an intervention, or potential complications from the AE, including prevention of greater severity or monitoring of the AE.

The ICH and FDA define ?hospitalization? as an indicator for seriousness. The Serious adverse drug experience definition (Code of Federal Regulations; Title 21, Volume 5; Revised as of April 1, 2008; CITE: 21CFR310.305) includes an experience that results in ??inpatient hospitalization or prolongation of existing hospitalization? and refers again to hospitalization in stating ?Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when??

For expedited reporting requirements, (CTEP, NCI Guidelines: Adverse Event Reporting Requirements Effective January 1, 2005} ?hospitalization? is specifically defined as follows: ?3.2.2 Expedited Adverse Event Reporting of Hospitalization or Prolongation of Existing Hospitalization for all Phases of Trials: CTEP defines hospitalization for expedited AE reporting purposes. Hospitalization is used as an indicator of the seriousness of the adverse event and should be reserved for situations where the adverse event truly fits this definition and not for hospitalizations associated with less serious events. For example, a hospital visit where a patient is admitted for observation or minor treatment (e.g., hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling, is not an AE, and therefore is not to be reported either as a routine AE or in an expedited report.?

What is ADL and what is the difference between instrumental ADL and self-care ADL?

ADL is Activities of Daily Living; it refers to the performance of the basic activities of self care. Adverse event assessment includes questions related to ADL to give an indication of the impact of a symptom (adverse event) on the patient?s ability to care for self in physical, mental, and social daily life.

Instrumental ADL refers to the ability to do shopping, laundry, finance, transportation, etc. Many CTCAE v4.0 Grade 2 descriptions include ?limiting instrumental ADL.?

Self-care ADL refers to getting in and out of bed, dressing, eating, getting around inside, bathing, using the toilet, etc. Many CTCAE v4.0 Grade 3 descriptions include ?limiting self care ADL.?

Why does CTCAE v4.0 list several Death AE terms when ICH and regulators define Death as an outcome?

Death as an AE term is a CTEP, NCI requirement because AE reporting is the primary mechanism for getting death information to CTEP, Investigational Drug Branch. Industry and other sponsors may choose to exclude death as an AE, but the CTEP processes necessitated inclusion of Death as an AE term in CTCAE.

The Death AE terms are:

- Death NOS (Not Otherwise Specified) - A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Sudden death NOS - An unexpected cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death neonatal - A disorder characterized by cessation of life occurring during the first 28 days of life.
- Fetal death - A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation.

Why is Grade 5 Death not associated with some AE terms?

Grade 5 is not appropriate for all AE terms. These general rules about Grade 5 apply in CTCAE v4.0:

- If an AE has no Grade 4, there can be no Grade 5.
- AEs with the SOC Investigations can have no Grade 5 except ?Other, specify? because death does not result from abnormal diagnostic tests themselves, but rather from the medical conditions that the tests detect. The medical conditions, listed as AEs in their appropriate disorder SOCs, may include a Grade 5 Death.

Why does CTCAE v4.0 include quantitative values and clinical findings as part of the grading scale in several SOCs?

In the SOC Investigations, the AE terms are diagnostic test names with qualifiers (e.g., increased, decreased, abnormal). The quantitative test results are specified in the grading scales where appropriate.

The medical conditions (e.g., hyper-, hypo-) that the diagnostic tests indicate are listed as AE terms in their appropriate disorder SOCs (e.g., Hyperkalemia = SOC Metabolism and nutrition disorders; Hyperthyroidism = SOC Endocrine). The grading scales for these medical conditions include both clinical findings and lab test quantitative values.
Besides the SOC Investigations, which SOCs include quantitative values of diagnostic tests as part of the grading?

SOC	AE Terms with Quantitative Values
Blood and lymphatic disorders	Anemia Bone marrow hypocellular Disseminated intravascular coagulation Hemolysis Leukocytosis Gastrointestinal disorders
General disorders and administration site conditions	Fever

	Hypothermia
Metabolism and nutrition disorders	Acidosis Alkalosis Hypercalcemia Hypocalcemia Hyperglycemia Hypoglycemia Hyperkalemia Hypokalemia Hypermagnesemia Hypomagnesemia Hypernatremia Hyponatremia Hypertriglyceridemia Hyperuricemia Hypoalbuminemia Hypophosphatemia

Which CTCAE 4.0 AE terms contain pediatric-specific references in their grading scales?

CTCAE AE terms and grades are generally applicable to all populations The following AEs have grading scales and/or definitions that explicitly reference pediatric values.

SOC	AE Term with Pediatric Reference
Ear and labyrinth disorders	Hearing Impaired
Injury, poisoning and procedural complications	Postoperative hemorrhage
Investigations	Weight gain, Weight loss
Renal and urinary disorders	Proteinuria
Vascular	Hypertension

In the SOC Investigations, AE term "Ejection fraction decreased," the severity grade definitions include a percentage drop from baseline values of resting ejection fraction. Does the percentage drop refer to absolute percentage points or relative percentage of the baseline value?

The drop refers to absolute percentage points. Therefore, if the baseline value is 65, the Grade 2 criterion of 10% - 19% drop from baseline would require a minimum drop to 55 and a maximum drop to 46. The Grade 3 criterion of >20% drop from a baseline of 65 would require a minimum drop to 45.